

# Association of Serum Levels of Vitamin D with Blood Pressure Status in Northern Iranian Population: The PERSIAN Guilan Cohort Study (PGCS)

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**Background:** Evidence in the last decades has indicated an association between vitamin D and cardiovascular risk factors including blood pressure. The present study aimed to determine whether serum 25-hydroxyvitamin D is independently associated with blood pressure in a large population-based study.

**Methods:** The study was based on subjects from PERSIAN Guilan Cohort Study (PGCS), a prospective, population-based cohort study in Guilan, Iran. In 9520 men and women, aged 35–70 years, serum 25-hydroxyvitamin D, systolic and diastolic blood pressure were measured. Multiple logistic and linear regression analyses were conducted with adjustments for demographic factors (age and gender), anthropometric characteristics (waist circumference and body mass index), lifestyle variables (physical activity, alcohol, and smoking consumption), and renal function (serum creatinine).

**Results:** Fully adjusted linear regression analyses revealed a weak but statistically significant negative association between serum 25-hydroxyvitamin D levels and systolic blood pressure ( $\beta = -0.02$ , 95% CI =  $-0.052$  to  $-0.0001$ , P-value = 0.04), whereas vitamin D status was not significantly associated with diastolic blood pressure ( $\beta = -0.01$ , 95% CI =  $-0.026$  to  $0.009$ , P-value = 0.3). Serum 25-hydroxyvitamin D status showed no significant association with the presence of hypertension (OR 1.09, 95% CI = 0.94 to 1.25 for the lowest (25OHD <12 ng/mL) versus the highest (25OHD  $\geq 20$  ng/mL) category).

**Conclusion:** Lower serum vitamin 25 (OH) D levels were associated with higher systolic blood pressure; however, it was not associated with diastolic blood pressure and presence of hypertension.

**Keywords:** vitamin D, blood pressure, Guilan cohort study, Iran

## Introduction

Vitamin D deficiency is prevalent in the Islamic Republic of Iran.<sup>1</sup> Vitamin D has been known to maintaining bone health and mineral homeostasis for many decades, but recent research has shown that vitamin D receptors are present on a wide range of tissues, including the myocardium and the endothelium, proposing a much wider variety of physiological functions for vitamin.<sup>2–4</sup>

Clinical and epidemiological evidence in the last decades has indicated an association between vitamin D and cardiovascular risk factors including blood pressure.<sup>5,6</sup> Evidence demonstrates that vitamin D may regulate blood pressure by direct vascular effect via vitamin D receptors on endothelial cells,<sup>7</sup> and regulating the renin-angiotensin system via effects on the juxtaglomerular apparatus.<sup>8,9</sup>

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Most observational studies found that low serum vitamin D levels are associated with the risk of hypertension,<sup>10</sup> and with higher rates of cardiovascular events<sup>11</sup> and increased mortality rates,<sup>12,13</sup> but this relationship disappeared after adjustment for confounding factors in some studies.<sup>14</sup> Although interventional studies have suggested that vitamin D supplementation may reduce mortality,<sup>15</sup> recent systematic reviews and meta-analysis on the effects of vitamin D supplementation on blood pressure reduction found weak evidence to support a small blood pressure lowering effects of vitamin D and thus advised against using as an antihypertensive agent.<sup>16,17</sup>

However, the association of vitamin D and blood pressure (BP) has been explored in previous studies, but the results are conflicting may be due to small sample sizes, study populations heterogeneity, and methodological differences. Thus, the present study was conducted to determine if the associations between blood pressure and vitamin D could be found in a large population-based study based on data from The PERSIAN Guilan Cohort Study (PGCS), a prospective, population-based cohort study in Guilan, Iran.

## Materials and Methods

### Study Population

The PERSIAN Guilan Cohort Study (PGCS) is a prospective, population-based cohort study in Guilan, the northern province of Iran, recruited between October 8, 2014, and January 20, 2017, as part of the Prospective Epidemiological Research Studies in Iran (PERSIAN).<sup>18</sup> The Climate of Guilan province based on the Köppen Climate Classification was humid subtropical climate and its Biotope was Forests and woodland.<sup>19</sup> There was one predominant ethnic group in this province, that was Gilaci20. Different districts of the province were chosen to include different socioeconomic status levels including urban areas and 39 villages. This area was selected due to its long-term population stability, high population density, a relative similarity in demographic and behavioral characteristics. The sampling and data collection methods have been previously described in detail.<sup>20,21</sup> In total, 9520 persons (aged 35–70 years) participated in the study. The study was approved by the local ethical committee and written informed consent was obtained from all participants.<sup>18</sup>

### Data Collection

#### Measurement of Vitamin D

Blood samples were collected from all individuals using Vacutainers (Greiner Bio-One International

GmbH, Kremsmunster, Austria). Whole blood samples were collected in EDTA (K3) tubes (Becton Dickinson, France). Serum 25-Hydroxyl vitamin D was determined by using a commercially available electrochemiluminescence immunoassay with Roche Elecsys 2010 and Cobas E411 auto analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

A level that was less than 12 ng/mL (30 nmol/L) was defined as vitamin D deficiency, 12 to 20 ng/mL (50 nmol/L) was defined as vitamin D insufficiency ( $\geq 20$  defined as vitamin D sufficiency) and greater than 100 ng/mL (250 nmol/mL) was defined as vitamin D toxicity.<sup>22</sup>

#### Measurement of Blood Pressure

Blood pressure (mmHg) was measured after 10-min rest period twice in the right arm with participants in a seated position, back supported and legs uncrossed in a quiet room after 10-min intervals, using Richter auscultatory mercury sphygmomanometers (MTM Munich, Germany).<sup>20</sup> The mean of the two measurements was used in the analyses.

Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg and/or a prior diagnosis of hypertension by a health professional or current use of antihypertensive drugs.<sup>18</sup>

#### Other Measurements

Information on potential confounding factors that may affect vitamin D status and Blood pressure and their association were collected. These variables were included demographic factors (age and gender), anthropometric characteristics, lifestyle variables (physical activity, alcohol, and smoking consumption), and renal function.

Anthropometric characteristics including weight (kg), height (cm), waist circumferences (cm) are measured using US National Institutes of Health protocols and have been previously described in detail.<sup>20</sup>

Smoking status was categorized as nonsmoker or current smoker (tobacco, cigarettes, hookah, cigar, and pipe), and alcohol consumption was classified as none or current use. The level of physical activity was estimated by metabolic equivalent rates (METs) of self-reported daily activities of participants that have been previously described in detail.<sup>23</sup> Renal impairment was assessed by serum creatinine ( $\mu\text{mol L}$ ).

### Ethical Consideration

The present study was approved by Ethics Committee of Guilan University of Medical Sciences (Ethic code: IR.GUMS.REC.1397.129)

## Statistical Analyses

Differences in Characteristics of the participants according to the vitamin D status (sufficient, deficiency, insufficiency) were analyzed using the chi-square test and ANOVA followed by a Bonferroni. Multiple linear regression analyses were performed to assess the associations between systolic or diastolic blood pressure (dependent variables) and vitamin D levels (independent variables). In addition, we used categorical vitamin D status to detect possible nonlinear relations. Logistic regression analyses were used to evaluate the associations between vitamin D status (independent variables) and the presence of hypertension (dependent variable). All regression analyses were adjusted for potential confounding by demographic factors (age and gender), anthropometric characteristics (waist circumference and BMI), lifestyle variables (physical activity, alcohol, and smoking consumption), and renal function (serum creatinine).

All analyses were performed with the use of SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A P-value of less than 0.05 was considered significant.

## Results

A total of 9520 women and men aged 35 years to 70 were included in this study. The mean age of the study population was  $51.45 \pm 8.9$  years and 46.5% of participants were men. About 45.7% of individuals were from urban areas. Forty-eight percent of the study participants were educated in high school or less. The mean serum 25-Hydroxyl vitamin D concentration of participants was  $21.75 \pm 12.3$  ng/mL in the study population. Characteristics of the study population according to 25-hydroxyvitamin D level are shown in Table 1. Vitamin D deficiency and insufficiency were found in 20.6% and 29% of subjects, respectively. Participants with vitamin D deficiency were younger, less educated, more likely to be women and rural residence, had a higher BMI and Waist circumference, and were less physically active.

The assessment of the associations between systolic or diastolic blood pressure and Serum 25-Hydroxyl vitamin D levels by multiple linear regression analyses have shown serum 25OHD levels were not statistically significantly associated with diastolic blood pressure unadjusted and after adjustment for potential confounders (Table 2). In

**Table 1** Characteristics of Study Population According to Serum 25-Hydroxyl Vitamin D Levels

Variables	Vitamin D Deficient ( $<12$ ng/mL (30 nmol/L))	Vitamin D Insufficient 12–20 ng/mL (30–50 nmol/L)	Vitamin D Sufficient $\geq 20$ ng/mL (50 nmol/L)	P-value*
<b>Number of participants (total=9520)</b>	<b>1957(20.6%)</b>	<b>2762(29%)</b>	<b>4801(50.4%)</b>	
Serum 25(OH)D (nmol/L)	$7.8 \pm 2.42$	$15.3 \pm 2.34$	$31.1 \pm 10.42$	$<0.001$
Age (year)	$49.2 \pm 8.36$	$50.7 \pm 8.61$	$52.7 \pm 9.07$	$<0.001$
Urban (%)	812(41.5%)	1319(47.8%)	2223(46.3%)	0.004
High school or less education level (%)	858(50.3%)	1107(47%)	1844(47.6%)	0.08
Male (%)	768(39.2%)	1375(49.8%)	2281(47.5%)	$<0.001$
BMI ( $\text{kg}/\text{m}^2$ )	$28.6 \pm 5.31$	$28 \pm 5.04$	$27.9 \pm 5.05$	$<0.001$
Waist circumference (cm)	$99.8 \pm 12.5$	$98.6 \pm 12.57$	$98.1 \pm 12.35$	$<0.001$
Physical activity (METs/hour/day)	$40 \pm 8.24$	$41.1 \pm 8.94$	$41.2 \pm 8.82$	$<0.001$
Use of alcohol (%)	241(12.3%)	428(15.5%)	733(15.3%)	0.003
Smoking (%)	403(20.6%)	696(25.2%)	1247(26%)	$<0.001$
Serum creatinine ( $\mu\text{mol}/\text{L}$ )	$0.85 \pm 0.15$	$0.89 \pm 0.17$	$0.91 \pm 0.15$	$<0.001$
Diastolic BP (mmHg)	$77.1 \pm 10.63$	$77.8 \pm 10.93$	$77.8 \pm 10.96$	0.02
Systolic BP (mmHg)	$117.8 \pm 15.98$	$118.8 \pm 16.98$	$119.1 \pm 16.98$	0.01
Use of anti-hypertensive medication (%)	409(20.9%)	615(22.3%)	1221(25.4%)	0.001
Hypertension (%)	556(28.4%)	849(30.7%)	1620(33.7%)	$<0.001$
Vitamin D supplementation use (%) <sup>a</sup>	147(7.5%)	252(9.1%)	383(8.2%)	0.09

**Notes:** Data are expressed as mean  $\pm$  standard deviation or number (percentages). \*Statistical significance based on the ANOVA for continuous variables or Chi-square test for categorical variables. <sup>a</sup>Vitamin D supplements use of at least monthly.

**Abbreviations:** 25(OH) D, 25-hydroxyvitamin D; BMI, body mass index; METs, metabolic equivalent rates.

contrast, higher 25OHD levels were associated with higher systolic blood pressure, and this association reversed and remained statistically significant after adjustment for demographic factors, anthropometric characteristics, life-style variables, renal function, and anti-hypertensive medication or vitamin D supplementation (Table 2). Fully adjusted regression coefficients for 25OHD in relation to systolic blood pressure were  $-0.02$  (P value= 0.04), it means an increase in serum 25OHD of 1 nmol/L was associated with a 0.02 mmHg decrease in systolic blood pressure (Table 2).

Thirty-one percent of the study population had hypertension. Non-linear association between vitamin D status and the presence of hypertension evaluated with Logistic regression analyses (Table 3). There was no significantly Non-linear association between Serum 25OHD status and the presence of hypertension in unadjusted logistic regression analyses and after adjustment for potential confounders (Table 3).

## Discussion

In this population-based study of 9520 women and men, there was a weak but statistically significant negative association between serum 25-hydroxyvitamin D levels and systolic blood pressure, which an increase in serum 25OHD of 1 nmol/L was associated with a 0.02 mmHg decrease in systolic blood pressure.

The observed association between serum 25-hydroxyvitamin D levels and systolic blood pressure is consistent with other studies finding.<sup>24–27</sup> The underlying mechanisms are maybe a potent endocrine suppressor effect of vitamin D on renin biosynthesis to regulate the renin-angiotensin system.<sup>28</sup> In addition, the vitamin D receptors (VDR) lacking in Mice have elevated

renin and angiotensin II production, leading to hypertension.<sup>29</sup> On the other hand, vitamin D is indirectly associated with blood pressure due to the role in the regulation of calcium absorption from the gut<sup>17</sup> and in the maintenance of calcium homeostasis via interaction with parathyroid hormone.<sup>30</sup> Interestingly, vitamin D seems to reduce free radicals local production, with benefits on vascular health.<sup>31,32</sup> However, this association may be confounding by UVA irradiation, as shown in a study that UVA irradiation of human skin was associated with a significant drop in blood pressure.<sup>33</sup>

In contrast, in the current study, vitamin D status was not significantly related to diastolic blood pressure. The evidence of evaluating the effectiveness of vitamin D supplementation in blood pressure reduction from a systematic review and meta-analyses of the randomized controlled trials have provided evidence of a small but statistically significant reduction in systolic blood pressure but not diastolic blood pressure<sup>34</sup> that was agreed with the present study's findings. The lack of association between serum vitamin D level and diastolic blood pressure in the present study was consistent with results in previous observational studies.<sup>35</sup> Also, no significant correlations were obtained between vitamin D level and blood pressure variables in a previous study including middle-aged hypertensive and high normal blood pressure patients.<sup>36</sup>

The current study revealed that Serum 25OHD status was not significantly related to the presence of hypertension. This result is broadly in line with those of previous studies,<sup>37,38</sup> although they contrast with the small association between Serum 25OHD status and presence of hypertension in some previous studies.<sup>10,39</sup> However, our analysis includes a much larger sample size than previous studies and controls potential confounders by advance analyses.

**Table 2** Associations of Serum 25-Hydroxyvitamin D with Systolic and Diastolic Blood Pressure from Linear Regression Analysis

Serum 25-Hydroxyvitamin D (nmol/L)	Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
	Regression Coefficients (B)	95% Confidence Interval.	P-value	Regression Coefficients (B)	95% Confidence Interval	P-value
Model 1 (unadjusted)	0.025	0.006 to 0.061	0.01	0.01	−0.008 to 0.027	0.31
Model 2 (adjusted for demographic factors)	−0.027	−0.065 to −0.008	0.01	−0.02	−0.037 to 0.002	0.07
Model 3 (additionally adjusted for lifestyle factors)	−0.024	−0.06 to −0.004	0.02	−0.015	−0.032 to 0.005	0.16
Model 4 (additionally adjusted for anthropometric factors)	−0.017	−0.051 to 0.005	0.1	−0.008	−0.025 to 0.011	0.46
Model 5 (additionally adjusted for medical factors)	−0.02	−0.052 to −0.0001	0.04	−0.01	−0.026 to 0.009	0.34

**Notes:** Model 1: crude model. Model 2: model 1 adjusted for age, sex, residency, and educational level. Model 3: model 2 additionally adjusted for physical activity (METs/hour/day), alcohol use, and smoking. Model 4: model 3 additionally adjusted for BMI and waist circumference (cm). Model 5: model 4 additionally adjusted for anti-hypertensive medication or vitamin D supplementation use and Serum creatinine.

**Table 3** Associations of 25-Hydroxyvitamin D Status with the Presence of Hypertension Using Logistic Regression Analysis

Models	Vitamin D Deficient (<12 ng/mL (30 nmol/L))	Vitamin D Insufficient 12–20 ng/mL (30–50 nmol/L)			Vitamin D Sufficient ≥20 ng/mL (50 nmol/L)		
		Odds Ratio	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Model 1 (unadjusted)	1	1.11	0.98 to 1.27	0.08	1.28	1.14 to 1.44	<0.001
Model 2 (adjusted for demographic factors)	1	1.06	0.92 to 1.23	0.38	1.02	0.89 to 1.17	0.72
Model 3 (additionally adjusted for lifestyle factors)	1	1.08	0.93 to 1.25	0.27	1.05	0.92 to 1.21	0.41
Model 4 (additionally adjusted for anthropometric factors)	1	1.1	0.95 to 1.28	0.18	1.1	0.96 to 1.27	0.14
Model 5 (additionally adjusted for medical factors)	1	1.1	0.94 to 1.27	0.21	1.09	0.94 to 1.25	0.22

**Notes:** Model 1: crude model. Model 2: model 1 adjusted for age, sex, residency, and educational level. Model 3: model 2 additionally adjusted for physical activity (METs/hour/day), alcohol use, and smoking. Model 4: model 3 additionally adjusted for BMI and waist circumference (cm). Model 5: model 4 additionally adjusted for anti-hypertensive medication or vitamin D supplementation use and Serum creatinine.

## Limitations of This Study

Cross-sectional design was the limitation of the current study, which did not permit us to determine the order of events. Also, we cannot completely exclude residual confounders, despite our detailed adjustment for confounding because our study was not randomized.

## Conclusion

In conclusion, the present population-based study demonstrated that lower serum vitamin 25 (OH) D levels were associated with higher systolic blood pressure; however, it was not associated with diastolic blood pressure and presence of hypertension. These findings must be confirmed in cohort studies and randomized clinical trials. The possible implication of the present study for clinical practice was special attention to serum vitamin D levels in hypertensive patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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